REMARKS

Status of the Claims

Claims 1-13 are pending in this application. No claims have been canceled, added or amended. Applicants submit the following arguments in support of the allowability of the claims.

Rejections under 35 USC 103(a)

The Examiner maintains the rejection of claim 1 under 35 U.S.C. 103(a) as obvious over Yamao USP 6,030,845 in view of the abstract of JP 60047962. The Examiner rejects claims 2 and 3 under 35 U.S.C. 103(a) as obvious over Yamao USP 6,030,845 in view of the abstract of JP 60047962 and further in view of Bester et al. The Examiner rejects claims 4-9 under 35 U.S.C. 103(a) as obvious over Yamao USP 6,030,845 in view of the abstract of JP 60047962 and further in view of U.S. Patents 5,527,714 to Kosako and U.S. Patent 4,851,329 to Cohen et al. Finally, the Examiner rejects claim 10 under 35 U.S.C. 103(a) as obvious over Yamao USP 6,030,845 in view of the abstract of JP 60047962 and further in view of U.S. Patent 4,830,969 to Holmes. These rejections are respectfully traversed. Reconsideration and withdrawal thereof are respectfully requested.

The Present Invention

Claim 1 relates to a whole blood immunoassay comprising the steps of:

mixing a whole blood sample with sensitized insoluble carrier particles to cause an immune agglutination;

diluting the resulting agglutination mixture with an aqueous solution containing an erythrocyte lysing agent to lyse erythrocytes; and

determining a degree of agglutination of the resulting whole blood sample.

Claim 11 relates to a whole blood immunoassay comprising the steps of:

mixing a whole blood sample, which comprises an antigen and an antibody, with immuno-sensitized insoluble carrier particles to cause an immune agglutination prior to adding a lysing agent;

diluting the resulting agglutination mixture with an aqueous solution containing an erythrocyte lysing agent to lyse erythrocytes; and

determining a degree of agglutination of resulting whole blood sample.

Request for Clarification of the Status of Claim 11

The Examiner is requested to clarify the status of claim 11, which was of record at the time that the Examiner issued the Advisory Action.

Distinctions Between the Present Invention and the Prior Art

The Examiner's attention is directed to the description at col. 5, lines 54-63 of the Yamao et al. reference as follows:

> 2) CRP Measurement Method
> 0.04 ml of human whole blood collected in a usual manner using an EDTA-2K anticoagulant was placed in cell **1**, and 0.5 ml of each of hemolysis regent aqueous solutions "a" to "g" shown in Table 1 was added to it, and the mixture was incubated at 37°C. for three minutes, and 1.5 ml of the anti-human CRP antibody sensitized latex suspension prepared in item **1**) above was added to it, and the change in its absorbance at 800 nm for 1 minute between 4 and 5 minutes after the reaction was initiated was determined.

This portion of the Yamao et al. reference teaches that each of the hemolysis reagent aqueous solutions "a" to "g" was added to the human whole blood and the mixture was incubated. Then, the immuno-agglutination reaction was carried out.

The Examiner's attention is directed to the description at col. 5, line 64 - col. 6, line 8 of the Yamao et al. reference as follows:

> Separately, a calibration curve of the above sample was prepared using a commercial latex inmmunoturbidimetry CRP measurement kit intended for use in examining plasma as its sample. FIG 3. shows a calibration curve prepared using the results obtained in the above CRP measurement,

> and a calibration curve excellent in sensitivity as shown in symbols "a" and "b" in the figure was obtained using whole blood lysed forcibly with pure water "an, saponin aqueous solution "b" etc. However, the results indicated that surface active agents "c" to "g" inhibit agglutination reaction and are thus not suitable for immunoreaction, as shown in the symbols "c" to "g" in the figure.

This portion of the Yamao et al. reference teaches that a calibration curve, which was excellent in sensitivity, was obtained when the whole blood was hemolysed with pure water "a" or saponin aqueous solution "b." However, the agglutination reaction was inhibited when the whole blood was hemolysed with each of the surface-active agents "e" to "g."

More specifically, the Yamao et al. reference discloses a technique where the whole blood is first hemolysed and the antibody sensitized insoluble carrier particles are then added thereto. The mixture is then subjected to the immuno-agglutination reaction.

Accordingly, based upon the teachings of the Yamao et al. reference, one of ordinary skill in the art would conclude that it necessarily follows [e.g. it can not be avoided] that the agglutination reaction is inhibited by the surface-active agents "e" to "g" referred to above.

In contrast to the teachings of the Yamao et al. reference relied upon by the Examiner, the present invention recites that the whole blood sample is first subjected to the agglutination reaction.

Then, the hemolysis is carried out to prepare a sample for measurement.

The Examiner consistently insists on a showing unexpected results. However, such a showing is only required when the Examiner establishes a prima facie case of obviousness. In the present situation, the Examiner concludes that unexpected results are required because "it has been held that the use of known reagents to produce the results taught by the prior art is obvious. Merely arranging the steps of a known process without a showing of unexpected result does not read over the prior art teaching." This is the Examiner's presumably strongest position as it is set forth as argument "A" on page 9 of the attachment to the Advisory Action. This reasoning fails for both technical and legal reasons.

First, the Examiner's position legally fails because the Examiner has not established a prima facie case of obvious. See MPEP 2142 and 2143.

Second, the Examiner does not refer to either the MPEP or to case law to support her argument that "it has been held..." What is the Examiner's legal basis for her position? Again, the Examiner's position legally fails because the Examiner has not established a prima facie case of obvious.

Third, the Examiner's position technically fails for the technical (e.g. scientific) reasons argued above. Thus, the Examiner has not established a prima facie case of obvious.

Fourth, the prior art teaches away from modifying the references in the manner suggested by the Examiner, as pointed out above. See MPEP 2143.01.

Fifth, modifying the teachings of the references in the manner suggested by the Examiner would destroy the intended purpose or function of the reference. See MPEP 2143.01.

Accordingly, the Examiner's position represents impermissible hindsight and the rejections must be withdrawn.

With respect to "evidence" requested by the Examiner, such evidence is entirely unnecessary when the Examiner fails to establish a prima facie case of obviousness.

The Examiner's attention is directed to the Example of the present specification. The Example demonstrates that the antigen-antibody reaction was not inhibited by the surface-active agent [i.e. sodium dodecyl sulfate] used for hemolysis. In contrast to these results obtained by the present inventors in the Example of the present specification, Applicants also demonstrated that the antigen-antibody reaction was inhibited by a surface active agent in the method where the whole blood was first hemolysed by using a surface active agent, the antibody sensitized insoluble carrier particles were added thereto and then the mixture was subjected to the immuno-agglutination reaction as described on page 12, line 18 - page 14, line 15 of the specification, which is herein incorporated by reference.

The Examiner should further note that "sodium dodecyl sulfate" used in the Example of the present invention is the same product as "sodium lauryl sulfate" described as the anionic surface active agent "f" in Table 1 at col. 3 of the cited Yamao et al. reference.

Accordingly, it is readily apparent that the effect of the present invention cannot be achieved by the Yamao et al. reference when the above-mentioned surface-active agent is used as a hemolysing agent and the desired effect is neither taught nor suggested by Yamao et al. in combination with any of the cited references.

The Examiner should further note that none of the secondary references corrects the deficiency of the primary reference. For example, JP 60-47962 to Ito describes that the hemolysing agent may be added to the whole blood prior to the agglutination reaction or may be added to a suspension of the antibody or antigen-sensitized carriers. This means that the hemolysis is carried out prior to or in the course of the agglutination reaction. Accordingly, the present invention, in which the agglutination reaction is carried out prior to the hemolysis of the whole blood, is not taught or suggested by the combination of Yamao et al. in view of Ito.

Further, only saponin is actually used as a hemolysing agent in the Ito reference even though Ito describes that saponin or various kinds of surface-active agents can be used a hemolysing agent. Saponine is a hemolysing agent that does not have the technical

problem of inhibiting the agglutination, as Yamao indicates. Therefore, the Ito reference does not teach or suggest that the agglutination reaction is inhibited by the surface-active agent such as sodium dodecyl sulfate when used as a hemolysing agent.

In summary, the combination of references does not teach or suggest the effect of the present invention. The prior art does not recognize the problem where an agglutination reaction is inhibited by a surface-active agent (e.g. sodium dodecyl sulfate) when used as a hemolysing agent. The prior art does not recognize that this problem is solved and can be avoided by carrying out the agglutination reaction prior to hemolysis.

The Examiner cites Bester for disclosing optimization of the lysing agent, such as SDS. Bester also fails to disclose having agglutination occur prior to lysis. Inasmuch as Bester fails to compensate for the deficiencies in Yamao '845 and JP '962, as pointed out above, Applicants submit that this rejection should also be withdrawn for the reasons stated above.

The Examiner cites Kosako '714 and Cohen '329 for teaching the step of determining the concentration of particles to have an assay with high sensitivity and specificity. Inasmuch as Kosako '714 and Cohen '329 fail to compensate for the deficiencies in Yamao '845 and JP '962, as pointed out above, Applicants submit that this rejection should also be withdrawn for the reasons stated above.

The Examiner relies on Holmes '969 for disclosing the reaction time and temperature. Holmes '969, however, fails to disclose a whole blood immunoassay where agglutination takes place prior to hemolysis. As such, Applicants submit that Holmes '969 also fails to compensate for the deficiencies in the primary and secondary references, Yamao '845 and JP '962, as pointed out above. Therefore, this rejection should be withdrawn.

Conclusion

As Applicants have addressed and overcome all rejections in the Office Action, Applicants respectfully request that the objections and rejections be withdrawn and that the claims be allowed.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____

Marc S. Weiner, #32,181
P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

MSW/sh
0397-0431P

Attachment(s)